04/469,492

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/469,492	06/06/95	WEINER H	1010/16959-U

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EXAMINER	
[illegible]	
ART UNIT	PAPER NUMBER
1645	16

DATE MAILED: 11/09/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

[X] Responsive to communication(s) filed on 8/18/98

[X] This action is **FINAL**.

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

[X] Claim(s) 37-39, 42-49, 52-57 and 59-65 is/are pending in the application.
Of the above, claim(s) ______ is/are withdrawn from consideration.
[ ] Claim(s) ______ is/are allowed.
[X] Claim(s) 37-39, 42-49, 52-57 and 59-65 is/are rejected.
[ ] Claim(s) ______ is/are objected to.
[ ] Claim(s) ______ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[ ] The drawing(s) filed on ______ is/are objected to by the Examiner.
[ ] The proposed drawing correction, filed on ______ is [ ] approved [ ] disapproved.
[ ] The specification is objected to by the Examiner.
[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been

[ ] received.
[ ] received in Application No. (Series Code/Serial Number) ______.
[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: ______.

[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[X] Notice of Reference Cited, PTO-892
[ ] Information Disclosure Statement(s), PTO-1449, Paper No(s). ______
[ ] Interview Summary, PTO-413
[ ] Notice of Draftperson's Patent Drawing Review, PTO-948
[ ] Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Response to Amendment

1. The amendment filed 8-18-98 has been entered into the record. Claims 37-39, 42-49, 52-57 and 59-65 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. The rejection of claims 48-49, 52-55, and new claims 56, 62, 63, and 64 under 35 U.S.C. 102(b) as being anticipated by the Merck Manual is withdrawn based on applicants' amendment.

4. Claims 37-39, 42-49, 52-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Rejections Maintained

5. The rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 under 35 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 37-58 in Paper No. 6, mailed 12-31-96.

Applicants arguments and evidence has been carefully considered as it applies to the instant claims and is not found to be persuasive. Dr. Malcolm Fletcher attests that the data are encouraging rather than ineffective as the examiner asserts because it reduces the attack rate. Dr. Fletcher attests that the apparent lack of results for "Myloral" (i.e. myelin basic protein) is due

to the lack of side effects of the drug and a strong placebo effect. This is not persuasive because the function of a "control" such as a placebo is to rule out effects due to controls. In Exhibit I, clearly the placebo works better than the drug, thus the skilled artisan can not rule out that the effect of the drug on autoimmune disease was "placebo". The data support the examiners position that the placebo was better than the drug itself and thus is ineffective. Dr. Fletcher also discusses the concomitant β-interferon use and conclude that the combination was better than the placebo in reducing attacks and attributes this to the Myloral. This is not persuasive because the specific combination is not claimed. The sole administration is claimed. Applicants arguments drawn to the combination of β-interferon and Myloral are not effective because this is not commensurate in scope with the claims which are drawn to the administration of a single reagent. The results submitted do not support applicants position, the treatment of MBP alone was no better than placebo. If a drug is not better than the placebo, it is not effective. The evidence of declaration is therefore not persuasive and the art does not reflect the correlation of the outcome in animal model (EAE model) with the human disease for the administration of the drug alone. Applicant's argue that the examiner states that the control was better than the drug. Applicants argue that this is an incorrect assessment since the declaration demonstrated that Myloral with B-interferon had fewer attacks than the control placebo and B-interferon. However, the claims are not drawn to combinatorial therapy with B-interferon, this evidence is not persuasive. Clearly, *when administered alone there was no statistically significant effect* between placebo and test drug. The examiner find the evidence of the declaration inconsistent with the animal studies, which demonstrated a clear and convincing statistically significant effect. In contrast the evidence provided no clear, convincing, statistically significant effect between Myloral alone and placebo alone has been demonstrated. Thus, the

examiner disagrees with the declarant opinion in regard to the consistency of the outcome in humans with the EAE animal studies for Myloral alone. The evidence provided by applicants is seen to support that examiners position that the EAE mouse is not reasonably predictive the human response for the claimed invention. Applicants argue that it is not appropriate to limit to a subset of patients who will benefit. This is not persuasive, as indicated by applicants beta-interferon is routinely given to multiple sclerosis patients, and thus the data do not make it clear that the combination of Myloral with beta-interferon is due to the effect of beta-interferon alone. Thus, the Myloral alone does not have usefulness by itself, only in combination for all the reasons previously set forth and set forth above.

Applicants also argue the Eishebarth declaration which states that the NOD mouse model is the best model of Type I diabetes available. As previously explained at length the evidence in the specification, in light of the Cohen reference, teaches that administration is effective to reduce insulitis and not treat diabetes Type I. Applicants argue that since the model is predictive for immunosuppressants it is predictive of bystanders. Applicants argue that the NOD mouse is predictive of human therapy and that the predictability of this model is strengthened by the fact that known therapies including immunosuppressive approaches that are effective in man have also been found to be effective in the NOD mouse mode. This is not persuasive because the agents and modes of administration of the art compounds are different than that which is claimed. The skilled artisan would have reason to doubt that the differences in chemical composition and mode of administration would unpredictably effect the outcome because: Mueller et al (The Journal of NIH Research, 6:,47-51, October 1994) clearly indicates that "....the dose, chemical, physical form, route and frequency of administration, inflammatory capacity, or immunogenicity of the immunizing preparation act in concert to determine whether the immune

responsiveness to an antigen will be enhanced or reduced as a result of immunization." (page 48, column 1, first full paragraph). Mueller et al also teaches that "T cell tolerance in vivo can depend on the regulation of T cell antigen responsiveness." and concludes that "..our ability to translate these data into a curative therapy for such diseases is hindered by gaps in our knowledge. It is difficult to predict what effect anergy induction might have on the behavior of autoimmune T cells because little information is available regarding the effect of anergy on T cell effector functions -- as opposed to its generally accepted ability to block the clonal expansion of T cells. This is an important issue because, in the clinic, patients tend to be treated only after evidence of autoimmune disease has appeared." (pages 49-50, see bridging paragraph). Thus, the art teaches that it is difficult to predict the outcome for any particular antigen form for any specific autoimmune disease given that the autoimmune disease is already in progress in the clinic. Applicants also argue that early onset type I diabetes can be treated with immunosuppressive agents, while later stage diabetics have totally lost beta cell function and can not be treated. This is not persuasive because the claims are not limited to early onset type I diabetics. Applicants also assert that the Bach article indicates that immunosuppressive agents can be used to treat overt type I diabetes, to prevent diabetes or induce remission. This is not persuasive because the drugs of Bach are not bystander antigens and do not induce specific tolerance. Unlike applicants specification, the generic immunosuppressive agents have been shown in controlled studies with randomized placebos and have studied need for insulin. Applicants specification only provides for suppression or reduction in insulitis and fails to support prevention of overt diabetes. Moreover, the Bach article supports the examiners position that treatment of insulitis is not predictive of treatment of overt diabetes. Table 1 on page 365 of the Bach paper clearly demonstrates that prevention with a wide variety of agents is not predictive of

treatment of overt diabetes, wherein only 5 agents that were successful for the prevention of diabetes when treatment started at less than 3 months of age were able to also treat overt diabetes. The agents which were effective in both models have no common structure or common target antigen. Thus, effects with one agent are not predictive of other agents. Importantly, in order to prevent disease onset (i.e. which is encompassed by treating) in these animal models the agent must have been given before 3 months of age and the claims are not so limited. In addition, tolerizing agents such as the antibodies taught by Bach are not effective after a certain period of time. In the discussion of a search for tolerance using antibodies, Bach teaches that anti-H-2 II monoclonal antibodies prevent the onset of IDDM when applied before two months of age; however the treatment is no longer effective if applied after two months of age. Thus, it is clear that the time period for administration for treatment or prevention is critical. Applicants have not taught the appropriate time period for prevention in a human. In addition, treatments associated with long term remission in mice, are not associated with the clearing of insulitis. In contrast to applicants assertions, overt diabetes treatment and insulitis treatment clearly do not move together as evidenced by the Bach article. Thus, treatment of insulitis is not predictive of treatment of overt diabetes and vice versa.

Applicants also provide evidence regarding an insulin peptide in the treatment of diabetes. This is not persuasive because *the claims specifically exclude autoantigens and insulin* and the studies use specific peptides in the NOD mouse and lack a correlation with humans. Moreover, the evidence which demonstrates the nasal use of a specific insulin peptide is not persuasive for the claimed subject matter. Thus, this evidence does not support the claimed subject matter.

Applicants note that the administration of glucagon in the NOD model as a bystander antigen. It is noted that a single bystander antigen (i.e. glucagon) does not support a broad claim to any bystander antigen for treatment of diabetes, and that GAD is specifically claimed as a treatment of diabetes (see claim 47).

Applicants argue that WO 88/10120 provides substantial unrebutted evidence that the suppression of autoimmunity can be induced after the onset of autoimmune responses. The data has been carefully considered but it fails to support a bystander antigen which is not an autoantigen. Clearly myelin basic protein is an autoantigen. The evidence fails to support a bystander antigen which is not an autoantigen. Moreover, the evidence of WO 88/10120 is provided in the EAE model. This model of autoimmune disease has been discussed in the office actions and it is the position of the office that the response in an EAE model is not reasonably predictive of an effect in humans for all the reasons set forth of record.

Applicants arguments are therefore not persuasive and the rejection is maintained.

6. The provisional rejection of claims 37-39, 42-49, 52-57 and 59-65 as previously applied to claims 37-58 as being obvious over 08/472,017 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

7. The provisional rejection of claims 37-45, 47-55, and 57 and new claims 59-65 as previously applied to claims 37-45, 47-55, and 57 as being obvious over 08/461,591 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

8. The provisional rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 as previously applied to claims 37-58 as being obvious over 08/461,662 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

9. The provisional rejection of 37-39, 42-48, 52-57 and new claims 59-65 as previously applied to claims 37-46 and 48-58 as being obvious over 08/468,996 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

10. Claims 60, 61, 63, 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in Paper No. 13, mailed 2/28/98.

Applicants assert that this term is conventional in the art. This is not persuasive because there is no definition in the art or in the specification, of what encompasses "substantially" in regard to purity or free from autoantigens. Thus, the metes and bound of the claims can not be ascertained.

Status of Claims

11. All claims stand rejected.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
November 9, 1998

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600